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Review Article

Molecular Crossfires between Inflammasome Signalling and Dietary Small Molecule Inhibitors in Neurodegenerative Diseases: Implications for Medical Nutrition Therapy

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Abstract: Neurodegenerative disorders are a range of debilitating conditions that manifest due to the progressive loss of neuronal cells in specific brain regions. Current therapeutic options are less than adequate in many respects. Protein misfolding and aggregation are hallmarks of the most common neurodegenerative disorders. Consequently, they elicit cellular homeostasis disruption, synaptic connection loss, and subsequent cellular apoptosis. In recent years, research has increasingly linked dysregulated inflammatory responses mediated by the inflammasome complex to several neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, Epilepsy, Huntington's disease, Autism, stroke etc. The inflammasome is a cytosolic multiprotein complex that is essential for innate immunity. Microglia are the primary cells expressing inflammasomes in the central nervous system, although astrocytes, neurons, and infiltrating myeloid cells can also express and activate inflammasomes. Regrettably, dysregulated inflammasome signaling upregulates the release of pro-inflammatory cytokines, as well as activating caspase-1. This process contributes to the continuation of neuroinflammation and subsequent damage to neurons. In this review of existing literatures, we collated empirical evidences about various inflammasome signaling pathways in selected neurological disorders. Majorly, we emphasised their influence on the advancement of diseases and neuronal cell death. Available empirical data showed that dietary small molecule inhibitors offer multi-targeted interactions to inhibit inflammasome signalling and upstream neuroinflammation. Notably, the baseline mechanisms involve suppression of free radicals, downregulating NF-κB and NLRP3 oligomerization, activating anti-inflammatory pathways, reducing ER stress, and modulating the Nrf2-ARE pathway. This shows promise for developing innovative medical nutrition therapies for various neurological conditions.

Keywords: Neurodegenerative Disorders, Inflammasome, Small Molecule Inhibitors, Medical Nutrition Therapy.

INTRODUCTION

Multiprotein complexes of the innate immune system found in the cytosol called inflammasomes trigger caspase-1 and other inflammatory caspases (Martinon *et al*., 2002). By helping the body fight against invading germs and identifying aberrant self-generated danger signals, the 700 kDa protein complex known as the inflammasome is essential to the immunological response (Nnah *et al*., 2020). The inflammasome is formed in large part by receptor proteins such as NLRP1,

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NLRP3, NLRC4, NLRP6, NLRP7, NLRP12, AIM2, and IFI16 (Schroder & Tschopp, 2010). Members of the Caspase family include effector proteins such Caspase-1, Caspase-4, Caspase-5, and Caspase-11 and linker proteins like ASC (Lamkanfi & Dixit, 2014).

Especially, infections may cause an inflammatory reaction when they enter the human body (Zoete *et al*., 2014). Intracellular infections are identified and endogenous danger signals known as damage-associated molecular patterns (DAMPs) are detected by the innate immune system (Guo *et al*., 2015). When activated, inflammasomes stimulate pyroptosis, a type of programmed cell death, and caspase-1-mediated synthesis and release of pro-inflammatory cytokines (De Miguel *et al*., 201). The reactions are directed especially at the proinflammatory cytokines IL-1 and IL-18, which do not have the signal peptide needed for traditional release (Cai *et al*., 2022). Moreover, the inflammasome can become active by microbial infections. Consequently, the host's defence mechanism may rapidly induce inflammatory reactions and prevent pathogen multiplication, (Lara-Reyna *et al.*, 2022). In addition to its well-known function in immunological defence against infections, recent studies have demonstrated that the inflammasome also significantly affects the control of inflammatory responses and cellular death (Tsuchiya, 2020). Canonical and noncanonical inflammasomes are distinguished by their ability to activate caspase-1. The receptor proteins NLRP1, NLRP3, NLRC4, NLRC6, and AIM2 make up canonical inflammasomes. Inflammatory reactions are started by Caspase-1, which these receptor proteins can activate. Additionally noncanonical inflammasomes can be activated by the activation of Caspase-4, Caspase-5, and Caspase-11, which can start a variety of immunological responses.

Inflammasome Signalling in the Central Nervous System

The central nervous system is a repository of important interleukins-1b and 18 functions. Numerous brain cell types express certain receptors that can set off inflammatory signalling pathways and cause cell death and neurological injury (Frederiksen *et al.*, 2019). Interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) levels have been raised in association with brain injury, neurodegenerative diseases, and infections of the central nervous system (CNS) (Rumbaugh & Nath, 2009). Turner *et al.*, (2014) reported that cytokines IL-1b and IL-18 are involved in cognitive functions, including learning and memory. Pathogenesis of illnesses caused by inflammasomes is also greatly influenced by the release of inflammatory mediators and damage-associated molecular patterns (DAMPs) during pyrolysis. Numerous neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis, have been shown to cause neuroinflammation and neuronal death by necroptosis and apoptosis (Zhang et al., 2017). It has been discovered that some central nervous system (CNS) cell types express components of inflammasomes. Neurones, astrocytes, perivascular CNS macrophages, oligodendrocytes, and endothelial cells are the cell types engaged in this process (as reviewed by Voet *et al*., 2019). More study is needed to determine exactly how localised inflammasome signalling in various brain cell types affects the general disease of the central nervous system (CNS).

Inflammasome Signalling in Traumatic Brain Injury

Recent empirical data has highlighted the importance of NLRP3 inflammasome's function in controlling neuroinflammation following traumatic brain injury (TBI). In a study, the expression of the NLRP3, ASC, and caspase-1 proteins significantly increased six hours following traumatic brain injury (TBI) (Irrera *et al*., 2020). Even seven days after the injury, the inflammasome biomarkers continued to be at higher levels. Caspase-1, interleukin-1, and NLRP3 levels have been elevated in animal models of TBI at 12 and 24 hours after the damage (Postolache *et al*., 2020). The observation was in favour of the hypothesis that inflammatory cytokines are produced more when traumatic brain injury (TBI) triggers the NLRP3 inflammasome (Chakraborty *et al*., 2021). In addition, human patients with severe TBI expressed more IL-1, IL-18, caspase-1, and NLRP3. In their investigation on severe traumatic brain injury (TBI) in paediatric patients, Wallisch *et al*., (2017) found a notable rise in NLRP3 expression. Neonatal neuroinflammation has been observed to be associated with poor treatment outcomes and worsening of the illness. Postolache *et al*., (2020) have previously shown a correlation between increased levels of interleukin-1 (IL-1) in the CSF fluid and NLRP3 activation following traumatic brain injury (TBI). have noted this association in both adult and paediatric individuals.

Damage-associated molecular patterns (DAMPs) are priming signals released by brain tissue in situations of traumatic brain injury. Through the Toll-like receptor (TLR)/nuclear factor (NF-)B pathway, these signals trigger NLRP3 and pro-IL-1 (Chakraborty *et al*., 2023). Primed NLRP3 inflammasome sensors oligomerize. The creation of a fully assembled NLRP3 inflammasome complex results from the recruitment of ASC and pro-caspase-1 by this mechanism. Activating signals include reactive oxygen species produced by mitochondrial damage, calcium influx upon glutamate binding to NMDAR/AMPAR receptors, potassium extrusion through purinergic P2X7 receptor channels following ATP activation, and lysosome destabilisation (Kattan *et al*., 2023).

Inflammasome activation in multiple sclerosis and experimental autoimmune encephalomyelitis

The main central nervous system chronic inflammatory illness is called multiple sclerosis (MS). Peripheral immune cells can reach the brain when the blood-brain barrier (BBB) breaks down in the setting of

multiple sclerosis (MS) (Cui *et al*., 2022). Increased inflammation, demyelination, and neurodegeneration follow from the activation of local microglia and astrocytes by this event. Significantly, experimental autoimmune encephalomyelitis (EAE) has been linked to the pathogenesis by both IL-1β and IL-18 (Lin & Edelson, 2017). The bulk of research on inflammasomes in MS has been on the process by which macrophages and lymphocytes infiltrate the central nervous system during the course of the disease. Increased levels of caspase-1, IL-18, and IL-1b are seen in both cerebrospinal fluid (CSF) and peripheral blood mononuclear cells (PBMCs) in patients with multiple sclerosis (MS) (Huang *et al*., 2004). Furthermore, earlier research has shown that those with this disorder have higher levels of NLRP3 inflammasome-activating damage-associated molecular patterns (DAMPs) including ATP and uric acid, and they also have increased caspase-1 expression in both acute and chronic demyelinating lesions (Barclay & Shinohara, 2017).

Voet *et al*., (2018) have provided genetic data to highlight the significance of inflammasome signalling in microglia and border-associated macrophages during experimental autoimmune encephalomyelitis (EAE). The experimental autoimmune encephalomyelitis (EAE) in mice was shown to worsen when A20 was deleted in microglia and central nervous system (CNS) macrophages (Voet *et al*., 2018). The effect was seen to be caused by NLRP3 being overactivated, which increased central nervous system inflammation and the release of interleukin-1 beta (IL-1β). In the central nervous systems of patients with multiple sclerosis (MS) and animals with experimental autoimmune encephalomyelitis (EAE), McKenzie *et al*., (2018) found caspase-1- and GSDMD-mediated pyroptosis in microglia and myelin-forming oligodendrocytes.

Animal models of demyelination generated by cuprizone revealed delayed demyelination, loss of oligodendrocytes, and neuroinflammation in mice lacking NLRP3. This find emphasises the significance of the NLRP3 inflammasome in connection to multiple sclerosis. Once cuprizone was given, different effects of IL-1b and IL-18 on remyelination were noted. Animals deficient of IL-1b showed a delayed process of remyelination. By comparison, IL-18 has been shown to hasten remyelination (Jha *et al*., 2010).

Inflammasome activation in stroke

A major contributing element to stroke pathophysiology is acknowledged to be neuroinflammation, especially the cytokine IL-1b (Jayaraj *et al*., 2019). In one study, postmortem brain tissue from stroke patients had higher expression of NLRP3 and NLRP1, as well as cleaved caspase-1, IL-1b, and IL-18. In rats deficient in IL-1a/b, Boutin *et al*., (2001) found a steady decrease in ischemic infarct volumes during transient middle cerebral artery occlusion (MCAO). Improved clinical results in stroke models have been demonstrated by several research that have manipulated the NLRP3 pathway in mice. This was accomplished by NLRP3 knockout, MCC950/CRID3 suppression of the NLRP3 inflammasome, and intracerebroventricular injection of NLRP3 siRNAs (Anderson *et al*., 2023) among other approaches.

Inflammasome activation in Alzheimer's disease

A common neurodegenerative condition linked to ageing, Alzheimer's disease (AD) is typified by a slow loss of memory and cognitive ability (Chin *et al*., 2013). Alzheimer's disease (AD) is now recognised as the main cause of dementia and a significant contributing factor to mortality in cohort ageing studies. Extracellular senile plaques largely made of Aβ and intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau are hallmarks of Alzheimer's disease (AD) (Zhang *et al*., 2017). One of the main factors in the pathogenesis of Alzheimer's disease (AD) is recognised to be neuroinflammation (Johnson *et al*., 2021).

Mainly responsible for neuroinflammation in Alzheimer's disease are microglia in the central nervous system. Because they phagocytose, microglia are known to help heal damage caused by Alzheimer's disease. It should be mentioned, therefore, that an accumulation of Ab may cause microglial cells to become more active and release inflammatory mediators (Ibrahim *et al*., 2023).

According to the literature (Sanchez-Mico *et al*., 2021) the buildup of Ab may reduce the phagocytic ability of microglial cells. Other central nervous system (CNS) cells may be impacted by neuronal damage and synaptic dysfunction brought on by microglial inflammation (Colonna & Butovsky, 2017). A link has been found recently between the onsite of Alzheimer's disease and inflammasomes. IL-1b expression in microglia close to amyloid-beta plaques has been observed to be higher in Alzheimer's disease patients (Wang *et al*., 2015). Liang *et al*., (2022) reported that among AD patients, IL-1b, IL-18, NLRP3, and ASC expression was increased. Importantly, a particular subset of Alzheimer's disease patients has shown elevated expression of the NLRC4 and ASC inflammasome in their brain tissue (Liu & Chan, 2014; Saadi *et al*., 2020). The brains of Alzheimer's disease (AD) patients have been duly reported to express NLRP1. A considerable neuronal loss in the hippocampus of AD patients has been linked to NLRP1 activation (Španić *et al*., 2022). Furthermore, studies have revealed that the microglia phagocytose fibrillar Ab and activate caspase-1 (Codolo *et al*., 2013), activate the NLRP3 inflammasome, and release IL- TLR2 and TLR5 ligation by α-synuclein assembly (Scheiblich *et al*., 2021). Meanwhile, NLRP3 deficiency was shown to significantly improve hyperactive behaviour and spatial memory impairments in the transgenic APP/PS1 mouse model of AD (Heneka *et al*., 2013). Concurrent with this

improvement were lower levels of pro-inflammatory cytokines, smaller plaque sizes, less amyloid-beta (Ab) buildup in the hippocampus and cortex, and increased microglial phagocytic capacity. In the same study, the APP/PS1 model's caspase-1-deficient animals showed a similar behavioural trend. Moreover, cellular processes started by the NLRP3 inflammasome activation typically release apoptotic speck-containing particles (ASC) into the extracellular environment (Hulse & Bhaskar, 2022). Especially, these particles have the potential to be endogenous warning signals that might notify macrophages in the vicinity of cellular stress or injury (Akbal *et al*., 202). It has been shown, nevertheless, that ASC specks in the APP/PS1 AD model can physically interact with Ab, causing misfolded proteins to aggregate and plaques to form in a prion-like way (Biasizzo & Kopitar-Jerala, 2020). Furthermore reported in connection to Alzheimer's disease are the AIM2 inflammasomes (Wu *et al*., 2017; Severini *et al*., 2021).

Inflammasome activation in amyotrophic lateral sclerosis (ALS)

The neurological disease known as amyotrophic lateral sclerosis (ALS) is typified by the gradual loss of upper and lower motor neurons, which causes voluntary muscle atrophy and paralysis (Barclay & Shinohara, 2017). Notably, mutations in the SOD1 gene account for 20% of cases of familial ALS and have been applied to various ALS experimental models (Berdyński *et al*., 202). In microglia, mutant SOD1 has been demonstrated to activate caspase-1 and IL-1b (Crown *et al*., 2019). In the past, NLRP3, NLRC4, and AIM2 have been regularly shown to be expressed in the brain tissue of mutant SOD1 transgenic rats (Wuolikainen *et al*., 2012; Hummel *et al*., 2021; Huai & Zhang, 2019). Elevated levels of NLRP3, ASC, caspase-1, and IL-18 expression were found in the spinal cord tissue after death (Chen *et al*., 2021). The main cell type in the spinal cord expressing the NLRP3 inflammasome was found to be astrocytes (Al Mamun *et al*., 2019). The NLRP3 gene expression levels can be used as a biomarker to improve animal model diagnosis and prognosis of skeletal muscle diseases. In a clinical context, it can also make blood sample analysis easier to do to find signs of amyotrophic lateral sclerosis (Moreno-García *et al*., 201).

Inflammasome activation in Parkinson’s disease

Progressive neurodegenerative disease Parkinson's disease (PD) is typified by dopaminergic neuronal death in the substantia nigra pars compacta (Chen *et al*., 2020). A key clinical feature of the condition, Lewy bodies are intraneuronal collections of fibrillar a-synuclein (Uemura *et al*., 2023). In the serum of people with Parkinson's disease (PD), Zhou *et al*., (2016) detected elevated levels of caspase-1 and IL-1b (Stojakovic *et al*., 2017). Crucially, persistent production of IL-1b in the substantia nigra caused rats' motor deficits and a slow loss of dopaminergic neurons (Surmeier, 2018). NLRP3 inflammasome activation in response to a-synuclein has been demonstrated in human monocytes and BV2 microglial cells, but not in primary microglia (as reviewed by Voet *et al*., 2019). In a 2021 study, Mustapha and Taib found that mice lacking the NLRP3 gene lost nigral dopaminergic neurons when 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was administered. Reduced activation of caspase-1 and decreased IL-1b and IL-18 synthesis were linked to this finding. In cultured neurons, poisonous α-synuclein typically clumps following caspase-1 cleavage (Wang *et al*., 2016; Nuber & Selkoe, 2016). NLRP3 inflammasome signalling response was elevated in microglia and macrophages from PARK2 and PINK1 knockout mice as well as in people with PARK2 mutations (Mouton-Liger *et al*., 2018).

Inflammasome Signalling in Huntington's Disease

The neurodegenerative condition known as Huntington's disease (HD) is inherited autosomally dominant. Involuntary choreatic motions and cognitive and behavioural difficulties are two ways the illness may show up (Andhale & Shrivastava, 201). Many routes lead to the dysfunction and neuronal death brought on by the huntingtin gene mutation. The propensity of mutant huntingtin (mHTT) to form aberrant aggregates, mitochondrial function, synaptic function, transcription, translation, and cellular homeostasis are all profoundly influenced by mHTT (Rojas *et al*., 202). Patients with Huntington's disease (HD) have higher NLRP3 expression in peripheral blood mononuclear cells (PBMC) than do unaffected people (Holbrook *et al*., 2021). Supported by the higher levels of IL1ß detected in the plasma and particular brain areas of HD patients, the NLRP3 inflammasome is thought to be involved in the disease. Strong evidence suggests that, although both cytokines are released during NLPRP3 inflammasome activation, the secretion of IL-1 and IL-18 is controlled by different pathways (Tapia *et al*., 2019). The amounts of these inflammasome components increased most in the striatal spiny projection neurons and parvalbumin interneurons, which are more prone to degeneration in Huntington's disease (HD) (Paldino & Fusco, 202). Although striatal cholinergic interneurons are typically resistant to neurodegeneration associated with Huntington's disease, they have been shown to express NLPR3 inflammasome less than usual, with poly ADP ribose polymerase (PARP) enzymes helping to transfer this expression. Microglial activation in Huntington's disease patients has been shown in some investigations (Bertran-Gonzalez *et al*., 2012). Its correlations with cellular functions include inflammation, mRNA splicing, apoptosis, and cell proliferation (Sciacchitano *et al*., 2018). Increased Gal-3 expression in particular brain areas, such as the microglia caudate and putamen of people with Huntington's disease (HD), activates the NLRP3 inflammasome, which then causes the synthesis and release of interleukin-1 (IL-1) (Siew *et al*., 2019; García-Revilla *et al*., 2022; Ge *et al*., 2022).

Moreover, the growing recognition of mitochondrial dysfunction as a major factor in the onset of neurodegenerative diseases, such as Huntington's disease (Golpich *et al*., 2017). It is thought that misfolded protein aggregates—mHTT in particular—can damage microglial mitochondria and produce reactive oxygen species (ROS) and mitochondrial DNA (mtDNA) (Liu *et al*., 2017). Products associated with mitochondrial damage may be involved in the neuroinflammatory processes underlying Huntington's disease (Bono-Yagüe *et al*., 2020).

Dietary Small Molecule Inhibitors of Inflammasome

Naturally occurring bioactive compounds from edible foods are critical determinants of the remarkable therapeutic functions human nutrition (Adeoye *et al*., 2022a; Adeoye *et al*., 2022b). Distinctively, the expression of these natural products may either be peculiar to specific food variety or across various sources in the food chain with varying relative abundance (Adeoye *et al*., 2022c; Oyerinde *et al*., 2023). Interestingly, these nutraceuticals have been demonstrated to play notable molecular roles in altering the cause of different human diseases (David *et al*., 2022; Adetunji *et al*., 2022; Adeoye *et al*., 2023; Asiyanbola *et al*., 2024; Adetunji *et al*., 2024a). Notably, various essential nutrients have been identified as key players with remarkable antioxidant properties (Tijani *et al*., 2022; Olajide *et al*., 2023a), downregulating inflammatory responses (Olajide *et al*., 2023b), immunomodulatory activities and restoration of homeostasis (Adewole *et al*., 2023). Interestingly, diverse kinds of these nutraceuticals occur as small molecular weight compounds that can permeate the blood-brain barrier and confer neuroprotection (Adeoye *et al*., 2023; Opoggen *et al*., 2023 Adetunji *et al*., 2024b). Importantly, ROS is a critical damage-associated molecular pattern that may trigger downstream inflammasome activation. Therefore, a medical nutrition therapy that consist of predominantly antioxidative regimen may be highly beneficial for regulating the inflammasome and consequent inflammatory responses.

Due to the proven anti-inflammatory properties of certain naturally occuring compounds, these compounds could be used as additional treatments for various chronic human diseases that involve significant inflammation (Adetunji, *et al*., 2024c). Phytochemicals have been used to inhibit the NLRP3 inflammasome in many animal models of central nervous system diseases. Phytochemicals that reduce the synthesis of reactive oxygen species (ROS) can prevent the NLRP3 inflammasome from activating upstream (e.g., flavonoids, stilbenoids, and phenols) (Pellegrini *et al*., 2019). By preventing the activation of the inflammasome complex, reduced ROS levels may thereby lessen inflammation and neurodegeneration.

One important regulator of inflammatory reactions, NF-κB, may have its transcriptional activity directly blocked by certain bioactive components in food, which can also prevent the oligomerization of NLRP3. Both the inflammasome complex's construction and activation are prevented by this dual effect. Nutraceuticals such as curcumin (Olcum *et al*., 2020) and resveratrol (Tufekci *et al*., 2021), for example, have been demonstrated to inhibit NLRP3 oligomerization and transcription mediated by NF-κB, therefore lowering the biosynthesis of pro-inflammatory cytokines.

Among the anti-inflammatory pathways activated by nutraceuticals is the AMPK/SIRT1/PGC-1α pathway (Wiciński *et al*., 2023). ROS-detoxifying enzymes are increased and NLRP3 assembly is directly inhibited when these pathways are activated. This process favours longevity and cellular health in addition to lowering inflammation (Salminen *et al*., 2011). Resveratrol and curcumin, for instance, stimulate AMPK and SIRT1, thereby imitating the effects of calorie restriction and strengthening the endogenous antioxidant defences (Liu & Yu, 2021).

One such factor that activates the NLRP3 inflammasome is endoplasmic reticulum (ER) stress (Li *et al*., 2020). Inflammasome activation can be avoided by phytochemicals' ability to reduce ER stress. In neurological disorders where ER stress plays a role in the buildup of misfolded proteins and neuronal damage, this is especially pertinent. Sulforaphane (SFN) and other compounds have been demonstrated to prevent NLRP3 activation linked to ER stress, hence preventing neuroinflammation and neurodegeneration (Greaney *et al*., 2016).

Cellular antioxidant response depends critically on the Nrf2-ARE pathway (H. Liu *et al*., 2021). This pathway may be activated by nutraceuticals, which induces antioxidant proteins and phase II detoxification enzymes (Tőzsér & Benkő, 2016). Key factors in neurodegenerative disorders, inflammation and oxidative stress, are reduced in part by this activation. For example, it has been demonstrated that phytochemicals activating the Nrf2-ARE pathway reduce the expression of BACE1, an enzyme implicated in the synthesis of amyloid-beta peptides, therefore enhancing cognitive performance in AD models (He *et al*., 2023). A summary of dietary small molecule inhibitors of inflammasome activation is presented in Table 1.

Table 1.0: Dietary Small Molecule inhibitors of Inflammasome Signalling

S/N	Bioactive compound	Origin	Inflammasome inhibitory mechanisms	Reference
1	Mangiferin	Mangifera indica, *Cyclopia sp.*	Supresses the mRNA expression of interleukins, inhibiting NLRP3 inflammasome in an NF-κB-dependent manner	(Lei *et al*., 2021)
2	W-3-fatty acid	Sea foods	Prevents expression of NLRP3, AIM2, and NAIP5/NLRC4 inflammasomes	(Lin *et al*., 2017)
3	Apocynin (acetovanillone)	*Picrorhiza kurroa*	Curtailing oxidative stress, Effectively inhibiting NLRP3 inflammasome activation and NF-κB signalling	(Jin *et al*., 2019, Tayman *et al*., 2021; Wang *et al*., 2021)
4	Ginsenoside	ginseng	Inhibiting microglia NLRP3 inflammasome signaling,	(Jin *et al*., 2022)
5	salidroside	*Rhodiola sacinehalnsis, Rhodiola rosea, Rhodibetic tibetica, Ligustrum lucidum*	Inhibits the activation of NLRP3 inflammasome and apoptosis in microglia due to cerebral ischemia/reperfusion injury by blocking the TLR4/NF-κB signalling pathway. Inhibits NLRP3 induced pyrriptosis in Alzheimer's disease	(Liu *et al*., 2021; Cai *et al*., 2022)
7	Berberin	European barberry, Curcuma longa, Oregon grape,	Pathway inhibition of NLRP3 inflammasome activation	(Dai *et al*., 2022)
8	Resveratrol	Peanuts, grapes, blueberries, raspberries	Suppresses the activation of NLRP3 inflammasome-induced pyroptosis and the expression of miR-155 in microglia by modulating the Sirt1/AMPK pathway.	(Tufekci *et al*., 2021)
10	Vitamin D	Egg yolk, beef, liver	Inhibition of ROS/TXNIP pathway and activation of AMPK pathway Suppressing NLRP1	(Tunbridge & França Gois, 2020) (Nakajo *et al*., 2021)
11	Vitamin E	Essential oil	Inhibit TRAF/NFKB pathway and activate AMPR/autophagy axis	(Kim *et al*., 2016). (Dapueto *et al*., 2021)
12	Curcumin	Tumeric	modulation of NF-KB and interleukin secretion, NLRP3	(as reviewed by Olcum *et al*., 2020)
13	Hesperetin	Citrus sp., grape	AOPPs, 1ba-1, NLRP3, IL-1B, ROS, Nr-f2, Ho-1blocked the expression of NLRP3, Caspese-1, PL0ASC, IL-18, IL-1I	(Z. Liu *et al.*, 2023)
14	Sulforaphane	Broccoli	Suppresses the activity of several inflammasomes independent of Nrf2.	(Greaney *et al*., 2016)
15	Parthenolide	*Tanacetum pertherium* (fever few)	Downregulates NRP1, NRP3, NLRC4 Inhibiting NLRP3 ATPase activity	(Ding *et al*., 2022); (L. Liu *et al*., 2023)
16	Quercetin	*Citrus sp*., onion, apple, olive oil	Inhibits NLRP3 and AIM2, prevents microglial activation and ASC oligomerization	(Jiang *et al*., 2016); (Domiciano *et al.*, 2017), (Alattar *et al*., 2023).

CONCLUSION

The NLRP3 inflammasome plays a crucial role in the innate immune responses. Chronic inflammation is a significant concern for a range of neurodegenerative illnesses, with the overactivation of inflammasomes being a key factor in the advancement of these conditions. As a result, there are currently several investigations being conducted to reduce the NLRP3 inflammasome in order to prevent the inflammatory cause associated with neurodegenerative diseases. Extensive research has demonstrated the remarkable ability of these plant-based compounds to effectively inhibit inflammasomes and their related components. Many phytochemicals have the ability to decrease the NLRP3 inflammasome, although the precise mechanism behind this process is not fully understood. Further research is required to develop a treatment plan for inhibiting inflammasomes using a variety of plant-based compounds. Although laboratory and animal experiments have shown promising results, it is crucial

to conduct clinical trials that specifically focus on the NLRP3 inflammasome. This is crucial for the treatment of human ailments.

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